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# Health Effects Assessment for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin

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# HEALTH EFFECTS ASSESSMENT FOR 2,3,7,8-TETRACHLORODIBENZO-*P*-DIOXIN

U.S. Environmental Protection Agency
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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or $q_1^*$ values are determined for carcinogens for both oral and inhalation routes.

A $q_1^*$ was determined for 2,3,7,8-tetrachlorodibenzo-p-dioxin based on oral exposure.

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## PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1983b. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of 2,3,7,8-TCDD. Prepared by the Carcinogen Assessment Group, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984a. Health Assessment Document for Polychlorinated Dibenzo-p-Dioxins. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84-014A. NITS PB 84-220268.

U.S. EPA. 1984b. Ambient Water Quality Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-072.

U.S. EPA. 1985. Drinking Water Criteria Document on 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. (Final draft)

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is

assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, $q_1$*s have been computed based on oral and inhalation data if available.

## ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

2,3,7,8-TCDD has been shown to be carcinogenic in many independent rodent bioassays with oral exposure resulting in increases in incidence of a variety of tumor types. Results of *in vitro* mutagenicity tests have been mixed. Human exposure data suggest a link between 2,3,7,8-TCDD exposure and increased cancer incidence, but are inadequate for quantitative risk assessment. Using data for tumor incidence in female rats orally exposed to 2,3,7,8-TCDD, a carcinogenic potency for oral exposure to humans ($q_1^*$) of $1.56 \times 10^5$ $(mg/kg/day)^{-1}$ was estimated.

## ACKNOWLEDGEMENTS

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADI | Acceptable daily intake |
| AIC | Acceptable intake chronic |
| AIS | Acceptable intake subchronic |
| BCF | Bioconcentration factor |
| bw | Body weight |
| CAS | Chemical Abstract Service |
| CS | Composite score |
| $ED_{50}$ | Effective dose for 50% of recipients |
| GI | Gastrointestinal |
| LOAEL | Lowest-observed-adverse-effect level |
| LOEL | Lowest-observed-effect level |
| MED | Minimum effective dose |
| NOAEL | No-observed-adverse-effect level |
| PCDD | Polychlorinated dibenzo-*p*-dioxin |
| ppb | Parts per billion |
| ppm | Parts per million |
| ppt | Parts per trillion |
| TWA | Time-weighted average |

# 1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of 2,3,7,8-TCDD (CAS No. 1746-01-6) are given as follows (U.S. EPA, 1984a):

| | |
|---|---|
| Chemical class: | halogenated dibenzo-p-dioxins |
| Molecular weight: | 321.98 |
| Vapor pressure at 25°C: | $1.7 \times 10^{-6}$ (estimated) |
| Water solubility (at unspecified temperature): | 0.2 µg/ℓ |
| Octanol/water partition coefficient: | $1.4 \times 10^{-6}$ to $1.9 \times 10^{-7}$ (estimated) |
| BCF: | 5000 |
| Half-lives in | |
| Air: | unknown |
| Water: | 1-2 years |
| Soil: | 10-12 years |

No estimates of the half-life of 2,3,7,8-TCDD in the atmosphere are available. Based on the available information, photodegradation and wet and dry deposition of particle-bound 2,3,7,8-TCDD are probably the most significant fate-determining processes for atmospheric 2,3,7,8-TCDD (U.S. EPA, 1984a).

Based on the available data (U.S. EPA, 1984a), the possibility of vertical movement of 2,3,7,8-TCDD in soil in negligible under most conditions. Leaching of 2,3,7,8-TCDD from soil is possible under special conditions: for example, from sandy soils, particularly after multiple 2,3,7,8-TCDD application or accidental release of 2,3,7,8-TCDD on soil (U.S. EPA, 1984a).

## 2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

### 2.1. ORAL

The GI absorption of 2,3,7,8-TCDD is a function of both the dose administered and the vehicle used. Poiger and Schlatter (1980) reported a linear relationship between the dose of 2,3,7,8-TCDD and rat hepatic tissue levels of 2,3,7,8-TCDD over the range of 0.06-1.4 μg/kg bw. The percentage of the dose absorbed apparently decreased at doses higher than 1.4 μg/kg bw. Rose et al. (1976) estimated that steady-state concentrations would be reached within 13 weeks following gavage administration of 0.1-1.0 μg 2,3,7,8-TCDD/kg bw/day to rats for 5 days/week. Within the dosage range tested, the rate constant defining the approach to steady state was independent of the dosage. Fries and Marrow (1975) found that 2,3,7,8-TCDD at 7 or 20 ppb in the diet fed to rats for 6 weeks was 50-60% absorbed. Single or repeated (5 days/week for 7 weeks) doses given to rats by gavage in acetone:corn oil (2:25 or 1:9) were ~70-86% absorbed (Rose et al., 1976; Piper et al., 1973). A similar extent of absorption was reported in hamsters by Olson et al. (1980) who estimated absorption of a 650 μg/kg bw dose in olive oil at 74%. In guinea pigs, absorption was estimated at 50% [Nolan et al., 1979 (detail of protocol not provided)]. The data for rats suggest that a greater extent of absorption results from gavage rather than from dietary treatment, implying that adsorption to food particles may inhibit absorption. Adsorption on aqueous suspensions of soil has been shown to markedly reduce GI absorption (Poiger and Schlatter, 1980). Replacing soil with activated charcoal nearly eliminated absorption from the GI tract. Van der Berg et al. (1983) found lower hepatic levels of PCDD in rats fed for 19 days with a diet containing PCDD-laden fly ash than in rats fed an extract of fly ash containing PCDDs at comparable levels. The

differences in concentrations of PCDDs in the liver between fly ash and extract-fed rats were greater with the more highly chlorinated PCDDs than with 2,3,7,8-TCDD.

## 2.2. INHALATION

Pertinent data regarding to the absorption of 2,3,7,8-TCDD from the respiratory tract could not be located in the available literature.

## 3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

### 3.1. SUBCHRONIC

3.1.1. Oral. The subchronic oral toxicity of 2,3,7,8-TCDD is summarized in Table 3-1. Two studies have investigated the effects of very low doses of 2,3,7,8-TCDD. Murray et al. (1979) investigated the teratogenic and reproductive effects of dietary 2,3,7,8-TCDD (0, 0.001, 0.01 or 0.1 µg/kg bw/day) in Sprague-Dawley rats. The $F_0$ rats were maintained on the treatment diets for 90 days and were then mated twice, producing the $F_{1a}$ and $F_{1b}$ generations. The $F_{1b}$ and $F_2$ rats were mated at ~130 days of age, producing the $F_2$ and $F_3$ litters, respectively. The authors reported a NOAEL of 0.001 µg/kg bw/day for reduced fertility and fetal survival; however, Nisbet and Paxton (1982) reanalyzed the data from this study using different statistical techniques and concluded that a dose of 0.001 µg/kg bw/day resulted in a significantly reduced gestational index, decreased fetal weight, increased liver-to-body-weight ratios and an increased incidence of dilated renal pelvis.

Vos et al. (1973) measured the effect of eight weekly gavage doses of 0.008, 0.04, 0.2 or 1.0 µg/kg bw/week (equivalent to 0.0011, 0.0057, 0.029 or 0.143 µg/kg bw/day) on immune function in groups of 10 female Hartley guinea pigs. Effects on humoral immunity were measured by the response to a subcutaneous injection of tetanus toxoid, and cell-mediated immunity was measured by the delayed-type hypersensitivity to Mycobacterium tuberculosis. The lowest dose that produced a reduction in immune response was 0.0057 µg/kg bw/day, with a no-effect level of 0.0011 µg/kg bw/day.

3.1.2. Inhalation. No data on the subchronic inhalation toxicity of 2,3,7,8-TCDD were located in the available literature.

TABLE 3-1

Effects of Subchronic Oral Exposure to 2,3,7,8-TCDD[a]

| Species | Dose µg/kg/day | Duration of Exposure | Effect Level | Endpoints | Reference |
|---|---|---|---|---|---|
| Rat | 0.01 | 13 weeks | NOAEL | Decreased body weight | Kociba et al., 1976 |
| Rat | 0.1 | 13 weeks | LOAEL | Decreased body weight | Kociba et al., 1976 |
| Rat | 0.07 | 13 weeks | NOAEL | Toxic hepatitis | NTP, 1980 |
| Rat | 0.14 | 13 weeks | LOAEL | Toxic hepatitis | NTP, 1980 |
| Rat | 1.0 | 30 days | NOAEL | Decreased body weight | Harris et al., 1973 |
| Rat | 0.71 | 6 weeks | NOAEL | Decreased body weight | Harris et al., 1973 |
| Rat | 0.1 | 30 days | LOAEL | Thrombocytopenia | Zinkl et al., 1973 |
| Rat | 0.71 | 6 weeks | LOAEL | Decreased body weight and thymus weight | Vos et al., 1973 |
| Rat | 0.001 | 3 generations | LOAEL[b] | Decreased body weight, decreased fertility, decreased fetal survival | Murray et al., 1979 |
| Mouse | 0.014 | 13 weeks | LOAEL | Toxic hepatitis | NTP, 1980 |
| Mouse | 0.71 | 4 weeks | NOAEL | Porphyria | Goldstein et al., 1978 |
| Mouse | 3.57 | 4 weeks | LOAEL | Porphyria | Goldstein et al., 1978 |
| Mouse | 5.0 | 4 weeks | LOAEL | Decreased thymus weight and graft-versus-host response | Vos et al., 1973 |

TABLE 3-1 (cont.)

| Species | Dose µg/kg/day | Duration of Exposure | Effect Level | Endpoints | Reference |
|---|---|---|---|---|---|
| Mouse | 0.14 | 4 weeks | LOAEL | Decreased resistance to *Salmonella* | Thigpen et al., 1975 |
| Mouse | 0.21 | 4 weeks | LOAEL | Increased endotoxic (*E. coli*) susceptibility | Vos et al., 1978 |
| Mouse | 1.3 | 5 weeks | LOAEL | Decreased tetanus response, antigenic RBC response, sensitization to DNFB, resistance to *Salmonella* infection, resistance to *Listeria* infection | Hinsdill et al., 1980 |
| Guinea pig | 0.0011 | 8 weeks | NOAEL | Decreased body weight, thymus weight and tuberculin hypersensitivity | Vos et al., 1973 |
| Guinea pig | 0.0057 | 8 weeks | LOAEL | Decreased body weight, thymus weight and tuberculin hypersensitivity | Vos et al., 1973 |

[a]Source: U.S EPA, 1984b

[b]Reported as NOAEL by Murray et al. 1979; considered a LOAEL by Nisbet and Paxton (1982) during a reevaluation of the data.

RBC = red blood cells; DNFB = 2,4-dinitro, 1-fluorobenzene

## 3.2. CHRONIC

3.2.1. Oral. The chronic oral toxicity of 2,3,7,8-TCDD is summarized in Table 3-2. In rats, NOAELs for liver toxicity were noted at 0.001 (Kociba et al., 1978, 1979), 0.0014 (Goldstein et al., 1982; NTP, 1980) mg/kg/day. These levels resulted in evidence of liver toxicity in mice (NTP, 1980; Toth et al., 1978, 1979). In rats, levels of 2,3,7,8-TCDD in the ranges of 0.007-0.71 mg/kg/day were regarded as LOAELs (Goldstein et al., 1982; King and Roesler, 1974; Kociba et al., 1978, 1979; NTP, 1980; Cantoni et al., 1981).

Toth et al. (1978, 1979) administered weekly doses of 0.0, 0.007, 0.7 or 7.0 µg 2,3,7,8-TCDD/kg bw/week (TWA = 0.0, 0.001, 0.1 or 1.0 µg 2,3,7,8-TCDD/kg bw/day) to male Swiss mice by gavage for 104 weeks. Dermatitis and amyloidosis of the kidney, spleen and liver were observed at all dose levels. This study, therefore, establishes a LOAEL of 0.001 µg/kg bw/day.

3.2.2. Inhalation. No data pertinent to the chronic inhalation toxicity of 2,3,7,8-TCDD to experimental animals could be located in the available literature. The effects of occupational and environmental exposure of humans to 2,3,7,8-TCDD have been reported in a number of clinical case studies and epidemiology studies (U.S. EPA, 1984a,b,c, 1985). The exposures in these cases were probably predominantly by the inhalation and dermal routes. The major effects reported were chloracne, peripheral neuropathy, fatigue, eye irritation, headache, possibly increased incidences of birth defects and possibly tumors. No dose-response information was available from any of these studies.

## 3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral.. The teratogenicity of 2,3,7,8-TCDD-contaminated 2,4,5-T has been studied by a number of investigators (Table 3-3). Other investigators have studied the effects of purified 2,3,7,8-TCDD (Table 3-4).

TABLE 3-2

Effects of Chronic Oral Exposure to 2,3,7,8-TCDD*

| Species | Dose (µg/kg/day) | Duration of Exposure (weeks) | Effect Level | Endpoints | Reference |
|---|---|---|---|---|---|
| Rat | 0.0014 | 16 | NOAEL | elevated porphyrin levels | Goldstein et al., 1982 |
| Rat | 0.014 | 16 | LOAEL | elevated porphyrin levels | Goldstein et al., 1982 |
| Rat | 0.014 | 28 | LOAEL | fatty changes in liver, decreased body weight | King and Roesler, 1974 |
| Rat | 0.001 | 104 | NOAEL | degenerative and necrotic changes in the liver | Kociba et al., 1978, 1979 |
| Rat | 0.01 | 104 | LOAEL | degenerative and necrotic changes in the liver | Kociba et al., 1978, 1979 |
| Rat | 0.0014 | 104 | NOAEL | toxic hepatitis | NTP, 1980 |
| Rat | 0.007 | 104 | LOAEL | toxic hepatitis | NTP, 1980 |
| Rat | 0.71 | 45 | LOAEL | porphyria | Cantoni et al., 1981 |
| Rat | 0.0071 | 45 | LOEL | hepatic enzyme induction | Cantoni et al., 1981 |
| Mouse | 0.0014 | 104 | LOAEL | toxic hepatitis | NTP, 1980 |
| Mouse | 0.001 | 104 | LOAEL | dermatitis and amyloidosis | Toth et al., 1978, 1979 |

*Source: U.S. EPA, 1984b

TABLE 3-3

Studies on the Potential Teratogenic Effects of 2,3,7,8-TCDD-Contaminated 2,4,5-T*

| Species/ Strain | Route/ Vehicle | Form of 2,4,5-T | TCDD Level | Daily Dose | Treat-ment Days | Obser-vation Day | Maternal Response | Fetal Response | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Mice/ NMRI | rape-seed oil | acid | <0.02 ppm (Sample A) | 8, 15, 30, 45, 60,90 and 120 mg/kg | 6-15 | 18 | No toxic effects; decreased maternal weight at doses of 90 mg/kg and greater | Significant increases in the incidence of cleft palates at doses above 30 mg/kg (see text for additional details). Significantly decreased ($p<0.005$) fetal weight at all dose levels. | Neubert and Dillman, 1972 |
| | rape-seed oil | acid | 0.05±0.02 ppm (Sample B) | 30, 60 and 90 mg/kg | 6-15 | 18 | No toxic effects; decreased maternal weight at 90 mg/kg | Increases in the incidence of cleft palate at 60 and 90 mg/kg; significant ($p<0.005$) at all dose levels. | |
| | rape-seed oil | acid | NR (Sample C) | 90 mg/kg | 6-15 | 18 | No toxic effects but decreased maternal weight | Increase in the incidence of cleft palate; significant ($p<0.005$) decrease in fetal weight. | |
| | rape-seed oil | butyl ester | NR | 12 and 17 mg/kg | 6-15 | 18 | No toxic effects | Significant decrease in fetal weight but no effect on mortality; increase in the frequency of cleft palate similar to that seen with acid (see text). | |
| Mice/ NMRI | NR | acid | 0.05±0.02 ppm | 20, 35, 60, 90 and 130 mg/kg | 6-15 | NR | Toxic effects observed at 90 and 130 mg/kg | Increases in the percentage of resorptions and/or dead fetuses at 90 and 130 mg/kg; increases in the incidence of cleft palate and retardation of skeletal development at 35 mg/kg and above. | Roll, 1971 |
| Mice/ CD-1 | corn oil: acetone (9:1) | acid | <0.05 ppm | 115 mg/kg | 10-15 | 18 | No significant effect on weight gain or liver-to-body weight ratios | No effect on fetal mortality or fetal weight, but an increase in the incidence of cleft palate. | Courtney, 1977 |

TABLE 3-3 (cont.)

| Species/ Strain | Route/ Vehicle | Form of 2,4,5-T | TCDD Level | Daily Dose | Treat-ment Days | Obser-vation Day | Maternal Response | Fetal Response | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Mice/ C57Bl/6 | honey:water (1:1) | acid | 30 ppm | 46.4 and 113 mg/kg | 6-14 | 18 | NR | Significant ($p<0.01$) increases in the incidence of cleft palate in the high-dose group and cystic kidney in both dose groups; increased fetal mortality also observed in the high-dose group. | Courtney et. al., 1970a,b |
| Mice/ AKR | honey:water (1:1) | acid | 30 ppm | 113 mg/kg | 6-15 | 19 | Increase in liver-to-body-weight ratio. | Significant ($p<0.05$) increases in the incidence of cleft palate and fetal mortality | Courtney et. al., 1970a,b |
| Rats/ Sprague-Dawley (groups of 25 rats) | gavage/ hydroxy-propyl-methyl-cellulose | acid | 0.5 ppm | 1, 3, 6, 12, or 24 mg/kg/ day | 6-15 | 20 | No effect on body weight and no observable signs of toxicity. | A slight but statistically significant ($p<0.05$) decrease in implantations and litter size in lowest dose group only; no frank teratogenic effects based on a detailed examination of the control and 24 mg/ kg dose group; the only effect noted was an increase in the incidence of 5th partially ossified sternebrae. | Emerson et al. 1970, 1971 N.B. This appears to be a full publication of the abstract summary by Thompson et al., 1971 |
| Rats/ Wistar | gavage/ aqueous gelatin or corn oil | acid | <0.5 mg/kg | 25, 50, 100, or 150 mg/kg/ day | 6-15 | 22 | Some maternal mortality and decreased body weight gain at 150 mg/kg; no signs of toxicity at 100 mg/kg or below. | At 100 or 150 mg/kg, decreased fetal weight, increased fetal mortality and an increase of skeletal anomalies; no significant effect at the two lower dose levels. | Khera and McKinley, 1972; Khera et al., 1971 |
| | gavage/ aqueous gelatin or corn oil | butyl ester | <0.5 mg/kg | 50 or 150 mg/kg/day | 6-15 | 22 | NR | No significant effect on fetal morality, fetal weight, or the incidence of anomalies. | Khera and McKinley, 1972; Khera et al., 1971 |

TABLE 3-3 (cont.)

| Species/ Strain | Route/ Vehicle | Form of 2,4,5-T | TCDD Level | Daily Dose | Treatment Days | Observation Day | Maternal Response | Fetal Response | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Rats/ Holtzman | gavage/ 1:1 solution of honey and water | acid | 30 ppm | 4.6, 10.0 and 46.4 mg/kg/day | 10-15 | 20 | NR | Significant ($p<0.01$) increases in fetal mortality at the 2 higher dose levels; dose-related increases in the percent of abnormal fetuses per litter; a high incidence of cystic kidneys in treated groups. | Courtney et al., 1970a,b |
| Rats/ CD | gavage/ 15% sucrose solution | acid | 0.5 ppm | 10.0, 21.5, 46.4 and 80.0 mg/kg/day | 6-15 | 20 | Reduced maternal weight gain at the 2 higher dose levels ($p<0.05$) and increased liver-to-body-weight ratio at the highest dose level ($p<0.05$) | Increase in the incidence of kidney anomalies but no increase in cleft palate. | Courtney and Moore 1971 |
| Rats/ Sprague-Dawley | gavage/ methocellulose | acid | 0.5 ppm | 50 mg/kg | 6-15 | NS | No effect on mortality or body weight gain. | No significant effect on fetal mortality or fetal weight; a significant ($p<0.05$) increase in the incidence of delayed ossification. | Sparschu et al., 1971a |
| | gavage/ methocellulose | acid | 0.5 ppm | 100 mg/kg | 6-10 | NS | Increased mortality and decreased body weight gain. | Increase in the incidence of delayed ossification and poorly ossified or malaligned sternebrae ($p<0.05$) | Sparschu et al., 1971a |
| Syrian hamsters/ *Mesocricetus euratus* | gavage/ acetone, corn oil, and carboxymethyl cellulose in ratio of 1:5.8:10 | acid | <0.1-4.5 ppm | 20, 40, 80 and 100 mg/kg | 6-10 | 14 | NS | Dose-related increases in fetal mortality, gastrointestinal hemorrhages, and fetal abnormalities | Collins et al., 1971 |

*Source: U.S. EPA, 1985

NS = Not specified; NR = not reported

TABLE 3-4

Studies on the Potential Teratogenic and Reproductive Effects of 2,3,7,8-TCDD[a]

| Species/Strain | Vehicle | Compound | Daily Dose | Treatment Days | Observation Day | Maternal Response | Fetal Response | Reference |
|---|---|---|---|---|---|---|---|---|
| Mouse/C57Bl/6<br>Mouse/AKR | DMSO or honey:water (1:1) | 2,4,5-T containing 30 ppm TCDD | 21.5, 46.4, 113.0 mg/kg | 6-14 or 9-17 | 19[b] | Increased liver-to-body-weight ratio | Fetal death, cleft palate, cystic kidney | Courtney et al., 1970a,b |
| Mouse/CD-1<br>Mouse/DBA/2J<br>Mouse/C57Bl/6J | DMSO | 2,3,7,8-TCDD | 0.5, 1, 3 µg/kg | 6-15 | 17[b] or 18 | Increased liver-to-body-weight ratio | Cleft palate, kidney anomalies[c] | Courtney and Moore, 1971 |
| Mouse/C57Bl/6 | acetone: corn oil (1:9) | 2,3,7,8-TCDD | 1, 3 µg/kg | 10-13 or 10 | 18[b] | None reported | Cleft palate, kidney anomalies[c] | Moore et al., 1973 |
| Mouse/CD-1 | DMSO or corn oil | 2,3,7,8-TCDD | 25, 50, 100, 200, 400 µg/kg | 7-16 | 18[d] | Increased liver-to-body-weight ratio | Cleft palate, hydronephrotic kidneys, hydrocephalus, open eyes, edema, petechiae | Courtney, 1976 |
| Mouse/CF-1 | corn oil: acetone (98:2) | 2,3,7,8-TCDD | 0.001, 0.01, 0.1, 1.0, 3.0 µg/kg | 6-15 | 18[b] | None reported | Cleft palate, dilated renal pelvis | Smith et al., 1976 |
| Mouse/NMRI | rape-seed oil | 2,3,7,8-TCDD | 0.3, 3.0, 4.5, 9.0 µg/kg | 6-15 | 18 | No effect observed | Fetocidal at the high dose; cleft palate at doses at or above 4.5 µg/kg | Neubert and Dillman, 1972 |
| Rat/CD | DMSO | 2,3,7,8-TCDD | 0, 0.5, 2.0 µg/kg | 6-15, 9 and 10, or 13 and 14 | 20[b] | None reported | Kidney malformations at both dose levels | Courtney and Moore, 1971 |
| Rat/Sprague-Dawley | corn oil/ acetone | 2,3,7,8-TCDD | 0, 0.03, 0.125, 0.5, 2.0, and 8.0 µg/kg | 6-15 | 20[b] | Vaginal hemorrhage at 2.0 and 8.0 µg/kg | Intestinal hemorrhage at 0.125 and 0.5 µg/kg; fetal death at higher doses; subcutaneous edema | Sparschu et al., 1971b |

TABLE 3-4 (cont.)

| Species/Strain | Vehicle | Compound | Daily Dose | Treatment Days | Observation Day | Maternal Response | Fetal Response | Reference |
|---|---|---|---|---|---|---|---|---|
| Rat/Wistar | corn oil/ anisole | 2,3,7,8-TCDD | 0.0, 0.125, 0.25, 1, 2, 4, 8, 16 µg/kg | 6-15 | 22 | Maternal toxicity observed at or above 1 µg/kg | Increased fetal death observed at or above 1 µg/kg; subcutaneous edema and hemorrhages in the 0.25 µg/kg groups | Khera and Ruddick, 1973 |
| Rat/Sprague-Dawley | corn oil/ acetone (9:1) | 2,3,7,8-TCDD | 0.1, 0.5, 2.0 µg/kg | 1-3 | 21 | Decrease in body weight gain in the high-dose group | Decreased fetal weight in the 0.5 and 2 µg/kg group; cystic kidneys and dilated renal pelvis occurred in the 2 µg/kg group | Giavini et al., 1982a |
| Rat/Sprague-Dawley | diet | 2,3,7,8-TCDD | 0.001, 0.01 and 0.1 µg/kg[e] | throughout gestation | post-parturition | Low fertility at 0.01 and 0.1 µg/kg; decreased body weight at 0.01 and 0.1 µg/kg; dilated renal pelvis | Low survival at 0.01 and 0.1 µg/kg; decreased body weight at 0.01 slight dilated renal pelvis at 0.001 µg/kg | Murray et al., 1979 |
| Rabbit/ New Zealand | corn oil/ acetone (9:1) | 2,3,7,8-TCDD | 0.0, 0.1, 0.25, 0.5 and 1 µg/kg | 6-15 | 28 | Maternal toxicity at doses of 0.25 µg/kg and above | Increases in extra ribs and total soft tissue anomalies | Giavini et al., 1982b |
| Monkey/rhesus | diet | 2,3,7,8-TCDD | 8.6 pg/kg/day | 7 months prior to and during gestation | at term | 6/8 conceived; normal serum estradiol and progesterone | 3/8 normal births | Allen et al., 1979 |
| Monkey/rhesus | diet | 2,3,7,8-TCDD | 55.7 pg/kg/day | 7 months prior to and during gestation | at term | 3/8 conceived; decreased serum estradiol and progesterone | 1/8 normal births | Allen et al., 1979 |

[a]Source: U.S. EPA, 1985

[b]First day of gestation designated day 0.

[c]Kidney anomalies were not specifically defined.

[d]First day of gestation designated day 1.

[e]The high dose level (0.1 µg/kg/day) was discontinued due to very low fertility in adults.

DMSO = dimethyl sulfoxide

Neubert and Dillmann (1972) reported an $ED_{50}$ of 4.6 μg 2,3,7,8-TCDD/kg bw for the production of cleft palate in mice. Smith et al. (1976) reported a minimum effective oral dose of 1.0 μg 2,3,7,8-TCDD/kg bw/day for the production of teratogenic effects in CF-1 mice. Rats are less sensitive to the teratogenic effects of 2,3,7,8-TCDD; however, significant fetotoxic effects have been observed at doses of 1.0 μg/kg bw/day and higher (Giavini et al., 1982a, 1983; Khera and Ruddick, 1973; Khera et al., 1971; Khera and McKinley, 1972).

The teratogenic and reproductive effects of low doses of 2,3,7,8-TCDD have been investigated in a 3-generation reproduction study using 16 male and 32 female Sprague-Dawley rats/generation (Murray et al., 1979). The authors concluded that doses of 0.01 or 0.1 μg 2,3,7,8-TCDD/kg bw/day resulted in decreased fertility, decreased litter size and decreased fetal survival, and that 0.001 μg 2,3,7,8-TCDD/kg bw/day was a NOEL. Nisbet and Paxton (1982) reanalyzed these data using different statistical methods; they concluded that a dose of 0.001 μg 2,3,7,8-TCDD/kg bw/day significantly reduced the gestational index and fetal weights, and increased the liver-to-body-weight ratios and the incidence of dilated renal pelvis.

**3.3.2. Inhalation..** Pertinent data regarding the teratogenicity or other reproductive effects of inhalation exposure to 2,3,7,8-TCDD in experimental animals could not be located in the available literature. Several investigators have studied the incidence of birth defects in areas where 2,3,7,8-TCDD has been accidentally released or 2,3,7,8-TCDD-contaminated 2,4,5-T had been sprayed (U.S. EPA, 1979; Hanify et al., 1981; Field and Kerr, 1979; Nelson et al., 1979; Thomas, 1980; Department of Health, New Zealand, 1980; McQueen et al., 1977; Aldred, 1978; Townsend et al., 1982; Bonaccorsi et al., 1978; Bisanti et al., 1980; Reggiani, 1980). The individuals in these

studies were probably exposed by a variety of routes (inhalation, dermal, oral). Even in those studies in which a positive correlation between exposure and birth defects or abortions was found, 2,3,7,8-TCDD could not be unequivocally identified as the causative agent.

### 3.4. TOXICANT INTERACTIONS

2,3,7,8-TCDD is a potent enzyme inducer and, as such, may interact with a wide range of xenobiotics. These interactions can result in either inhibition or potentiation of the biological effects of the compounds that are substrates for these enzymes. Thus, 2,3,7,8-TCDD pretreatment alters the metabolism and reduces the carcinogenic potency of benzo[a]pyrene (Boobis and Nebert, 1976; Berry et al., 1976; Uotila et al., 1978). 2,3,7,8-TCDD pretreatment has also been demonstrated to alter the metabolism of aflatoxin $B_1$ (Gurtoo, 1980); nitrosamines (Scarpelli et al., 1980), N-2-fluorinylacetamide (DiGiovanni et al., 1979), 3,4-diaminisole (Reddy et al., 1980) and 7,12-dimethylbenz[a]-anthracene (DiGiovanni et al., 1979). Pretreatment with 2,3,7,8-TCDD also significantly alters the effects of the anesthetics zoxazolamine and hexabarbitone in rats (Greig, 1972).

## 4. CARCINOGENICITY

### 4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the oral carcinogenicity of 2,3,7,8-TCDD in humans could not be located in the available literature.

4.1.2. Inhalation. Several investigators have reported a possible link between occupational or environmental exposure to 2,3,7,8-TCDD and the development of tumors, mostly soft tissue sarcomas, lymphomas and stomach carcinomas (Holden, 1979; Cook et al., 1980; Moses and Selikoff, 1981; Honçhar and Halpern, 1981; Cook, 1981; Thiess and Frentzel-Beyme, 1977; Axelson and Sandell, 1974; Hardell, 1977; Axelson et al., 1979; Hardell and Sandstrom, 1979; Riihimake et al., 1980; Axelson et al., 1980; Eriksson et al., 1981; Hardell et al., 1981). The routes of exposure were probably mixed, but dermal and inhalation exposure would be expected to be the most common. Although the data are suggestive, the variety of compounds these populations were exposed to (short follow-up periods, self-selection and reliance on patients' recall to determine exposure and personal histories) limit the ability of these studies to link exposure to 2,3,7,8-TCDD unequivocally with induction of tumors in humans.

### 4.2. BIOASSAYS

4.2.1. Oral. The available data on the carcinogenicity of orally administered 2,3,7,8-TCDD are summarized in Table 4-1. Oral administration of 2,3,7,8-TCDD results in the induction of hepatocellular carcinoma in both sexes of mice and in female rats (Kociba et al., 1978; NTP, 1980; Toth et al., 1979), squamous cell carcinomas of the hard palate in both sexes of rats (Kociba et al., 1978), and follicular-cell adenomas of the thyroid in male rats and female mice (NTP, 1980). The studies of Toth et al. (1979) and Van Miller et al. (1977a,b) are of limited value for risk assessment

TABLE 4-1

Carcinogenicity Bioassays of 2,3,7,8-TCDD Administration by the Oral Route[a]

| Exposure Route | Species/ Strain | Sex | Dose or Exposure | Duration of Treatment | Duration of Study | Vehicle | Tumor Type | Tumor Incidence | p Value | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| Gavage | rats/ Osborne-Mendel | M | 0.0 µg/kg/week | 104 weeks | 105 weeks | corn oil-acetone (9:1) | follicular-cell adenomas of the thyroid, carcinoma of the thyroid | 1/69<br>0/69 | =0.006 | NTP, 1980 |
| | | | 0.01 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | follicular-cell adenomas of the thyroid, carcinoma of the thyroid | 5/48<br>0/48 | =0.042 | |
| | | | 0.05 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | follicular-cell adenomas of the thyroid, carcinoma of the thyroid | 6/50<br>2/50 | =0.021 | |
| | | | 0.5 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | follicular-cell adenomas of the thyroid, carcinoma of the thyroid | 0/50<br>1/50 | =0.001 | |
| Gavage | rats/ Osborne-Mendel | F | 0.0 µg/kg/week | 104 weeks | 105 weeks | corn oil-acetone (9:1) | neoplastic nodules of the liver, hepatocellular carcinoma of the liver | 5/75<br>0/75 | <0.001 | NTP, 1980 |
| | | | 0.01 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | neoplastic nodules of the liver, hepatocellular carcinoma of the liver | 1/49<br>0/49 | NS | |
| | | | 0.05 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | neoplastic nodules of the liver, hepatocellular carcinoma of the liver | 3/50<br>0/50 | NS | |
| | | | 0.5 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | neoplastic nodules of the liver, hepatocellular carcinoma of the liver | 12/49<br>3/49 | =0.006 | |

TABLE 4-1 (cont.)

| Exposure Route | Species/ Strain | Sex | Dose or Exposure | Duration of Treatment | Duration of Study | Vehicle | Tumor Type | Tumor Incidence | p Value | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| Gavage | mice/ $B6C3F_1$ | M | 0.0 µg/kg/week | 104 weeks | 105 weeks | corn oil-acetone (9:1) | hepatocellular carcinoma | 8/73 | =0.002 | NTP, 1980 |
| | | | 0.01 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | hepatocellular carcinoma | 9/49 | NS | |
| | | | 0.05 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | hepatocellular carcinoma | 8/49 | NS | |
| | | | 0.5 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | hepatocellular carcinoma | 17/50 | =0.002 | |
| Gavage | mice/ $B6C3F_1$ | F | 0.0 µg/kg/week | 104 weeks | 105 weeks | corn oil-acetone (9:1) | hepatocellular carcinoma, follicular-cell adenomas of the thyroid | 1/73<br>0/69 | =0.008<br>=0.016 | NTP, 1980 |
| | | | 0.04 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | hepatocellular carcinoma, follicular-cell adenomas of the thyroid | 2/50<br>3/50 | NS<br>NS | |
| | | | 0.2 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | hepatocellular carcinoma, follicular-cell adenomas of the thyroid | 2/48<br>1/47 | NS<br>NS | |
| | | | 2.0 µg/kg/week | 104 weeks | 107 weeks | corn oil-acetone (9:1) | hepatocellular carcinoma, follicular-cell adenomas of the thyroid | 6/47<br>5/46 | =0.014<br>=0.009 | |
| Oral | rat/ Sprague-Dawley | M | 0.0 ppb | 78 weeks | 95 weeks | in diet | all tumors[b] | 0/10 | NR | Van Miller et al., 1977a,b |
| | | | 0.001 ppb | 78 weeks | 95 weeks | in diet | all tumors[b] | 0/10 | NR | |

TABLE 4-1 (cont.)

| Exposure Route | Species/ Strain | Sex | Dose or Exposure | Duration of Treatment | Duration of Study | Vehicle | Tumor Type | Tumor Incidence | p Value | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| Oral (cont.) | | | 0.005 ppb | 78 weeks | 95 weeks | in diet | all tumors[b] | 5/10 | NR | Van Miller et al., 1977a,b |
| | | | 0.05 ppb | 78 weeks | 95 weeks | in diet | all tumors[b] | 3/10 | NR | |
| | | | 0.5 ppb | 78 weeks | 95 weeks | in diet | all tumors[b] | 4/10 | NR | |
| | | | 1.0 ppb | 78 weeks | 95 weeks | in diet | all tumors[b] | 4/10 | NR | |
| | | | 5.0 ppb | 78 weeks | 95 weeks | in diet | all tumors[b] | 7/10 | NR | |
| Oral | rat/ Sprague-Dawley | M | 0.0 µg/kg/day | 105 weeks | 105 weeks | in diet | squamous cell carcinoma of the hard palate, | 0/85 | NS | Kociba et al., 1978 |
| | | | | | | | squamous cell carcinoma of the tongue, | 0/85 | NS | |
| | | | | | | | adenoma of the adrenal cortex | 0/85 | NS | |
| | | | 0.001 µg/kg/day | 105 weeks | 105 weeks | in diet | squamous cell carcinoma of the hard palate, | 0/50 | NS | |
| | | | | | | | squamous cell carcinoma of the tongue, | 1/50 | NS | |
| | | | | | | | adenoma of the adrenal cortex | 0/50 | NS | |
| | | M | 0.01 µg/kg/day | 105 weeks | 105 weeks | in diet | squamous cell carcinoma of the hard palate, | 0/50 | NS | |
| | | | | | | | squamous cell carcinoma of the tongue, | 1/50 | NS | |
| | | | | | | | adenoma of the adrenal cortex | 2/50 | NS | |
| | | | 0.1 µg/kg/day | 105 weeks | 105 weeks | in diet | squamous cell carcinoma of the hard palate, | 4/50 | <0.05 | |
| | | | | | | | squamous cell carcinoma of the tongue, | 3/50 | <0.05 | |
| | | | | | | | adenoma of the adrenal cortex | 5/50 | <0.05 | |

TABLE 4-1 (cont.)

| Exposure Route | Species/ Strain | Sex | Dose or Exposure | Duration of Treatment | Duration of Study | Vehicle | Tumor Type | Tumor Incidence | p Value | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| Oral | rat/ Sprague-Dawley | F | 0.0 µg/kg/day | 105 weeks | 105 weeks | in diet | hepatocellular carcinoma, | 0/86 | NS | Kociba et al., 1978 |
| | | | | | | | squamous cell carcinoma of the tongue, | 0/86 | NS | |
| | | | | | | | squamous cell carcinoma of the lung | 0/86 | NS | |
| | | | 0.001 µg/kg/day | 105 weeks | 105 weeks | in diet | hepatocellular carcinoma, | 0/50 | NS | |
| | | | | | | | squamous cell carcinoma of the tongue, | 0/50 | NS | |
| | | | | | | | squamous cell carcinoma of the lung | 0/50 | NS | |
| | | | 0.01 µg/kg/day | 105 weeks | 105 weeks | in diet | hepatocellular carcinoma, | 2/50 | NS | |
| | | | | | | | squamous cell carcinoma of the tongue, | 1/50 | NS | |
| | | | | | | | squamous cell carcinoma of the lung | 0/50 | NS | |
| | | F | 0.1 µg/kg/day | 105 weeks | 105 weeks | in diet | hepatocellular carcinoma, | 11/49 | <0.05 | |
| | | | | | | | squamous cell carcinoma of the tongue, | 4/49 | <0.05 | |
| | | | | | | | squamous cell carcinoma of the lung | 7/49 | <0.05 | |
| Gavage | mice/ Swiss/H/ Riop | M | 0.0 µg/kg/week | 365 days | 588 days | sunflower oil | liver tumors[c] | 7/38 | NS | Toth et al., 1979 |
| | | | 0.007 µg/kg/week | 365 days | 649 days | sunflower oil | liver tumors[c] | 13/44 | NS | |
| | | | 0.7 µg/kg/week | 365 days | 633 days | sunflower oil | liver tumors[c] | 21/44 | <0.01 | |
| | | | 7.0 µg/kg/week | 365 days | 424 days | sunflower oil | liver tumors[c] | 13/43 | NS | |

TABLE 4-1 (cont.)

| Exposure Route | Species/ Strain | Sex | Dose or Exposure | Duration of Treatment | Duration of Study | Vehicle | Tumor Type | Tumor Incidence | p Value | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| Oral | mice/ Peromyscus polionotus | M and F | 0.0012 µg/kg/day | NA | NA | contaminated soil | liver | 0/15 | NS | Cockerham et al., 1980 |
| | | | 0.0 µg/kg/day | NA | NA | contaminated soil | liver | 0/15 | NS | |

[a]Source: U.S. EPA, 1985

[b]No single target organ for cancer was outstanding.

[c]Includes hepatomas and hepatocellular carcinomas.

NR = Not reported; NS = not significant

purposes because of the relatively short exposure times and small group sizes or both. The study in beach mice (Peromyscus poliontus) by Cockerham et al. (1980) was reported in insufficient detail (duration of treatment and observation periods were not reported). Treatment was in soil as a vehicle, a single low level was given, and negative results were obtained. The studies by Kociba et al. (1978) and NTP (1980) involved sufficiently long dosing schedules and large enough groups to be used for quantitative risk assessment.

Kociba et al. (1978) fed diets resulting in doses of 0.0, 0.001, 0.01 or 0.1 μg 2,3,7,8-TCDD/kg bw/day to groups of 50 male and 50 female Sprague-Dawley rats for 2 years. The control group consisted of 86 males and 86 females. Tumor incidences were significantly increased in both sexes in the high-dose group ($p<0.05$). The tumors observed were located in the hard palate, tongue and adrenal cortex of males and in the liver, tongue and lungs of females. The most common finding was hepatocellular carcinoma in the females, with incidences of 0/86, 0/50, 2/50 and 11/49 in the control, low-, mid- and high-dose groups, respectively.

The NTP, (1980) tested 2,3,7,8-TCDD for carcinogenicity in $B6C3F_1$ mice and Osborne-Mendel rats. Groups of 50 male and 50 female animals received 2,3,7,8-TCDD by gavage in corn oil:acetone (9:1), 2 days/week for 104 weeks. Male mice and male and female rats received 0, 0.01, 0.05 or 0.5 μg 2,3,7,8-TCDD/kg bw/week, and female mice received 0, 0.04, 0.2 or 2.0 μg 2,3,7,8-TCDD/kg bw/week. Control groups consisted of 75 vehicle treated and 75 untreated animals. In mice, statistically significant increases in hepatocellular carcinomas and neoplastic nodules were noted in the high dose-males, and increased incidences of hepatocellular carcinomas and adenomas, fibrosarcoma, histiocytic lymphoma, thyroid follicular-cell

adenoma and cortical adenoma or carcinoma were observed in high-dose females. A statistically significant increase in the incidence of follicular cell adenomas occurred in all treated groups of male rats, but the incidence did not occur in a dose-related fashion. Among female rats, significantly increased incidences of tumors occurred only in the high-dose group. These tumor incidences include subcutaneous tissue fibromas, adrenal cortical adenomas, and hepatocellular carcinomas and neoplastic nodules.

4.2.2. Inhalation. Pertinent data regarding the inhalation carcinogenicity of 2,3,7,8-TCDD could not be located in the available literature.

## 4.3. OTHER RELEVANT DATA

With few exceptions, 2,3,7,8-TCDD has not proven mutagenic in Salmonella typhimurium, either with or without metabolic activation (Table 4-2). The two positive tests with Salmonella were with TA1532, which is particularly sensitive to frame shift mutations. Positive results have been obtained in yeast in both in vitro assays using a metabolic activating system and host-mediated assays (Bronzetti et al., 1983). 2,3,7,8-TCDD has been shown to increase the frequency of reverse mutations in E. coli: $Sd^{-4}$ (Hussain et al., 1972). Hay (1982) reported positive results for transformation of baby hamster kidney cells as did Rogers et al. (1982) for mouse lymphoma cells. Khera and Ruddick (1973) reported negative results in the dominant lethal assay using Wistar rats. Conflicting results have been obtained from in vivo, in vitro and epidemiological investigations of chromosomal aberrations (IARC, 1977, 1982; Czeizel and Kiraly, 1976; Hay, 1978; Tenchini et al., 1979; Mottura et al., 1981; Green et al., 1977; Green and Moreland, 1975).

## 4.4. WEIGHT OF EVIDENCE

IARC (1982) considered the evidence for carcinogenicity to humans to be "inadequate," the evidence for carcinogenicity to animals to be "sufficient"

TABLE 4-2

The Results of Mutagenicity Assays in *Salmonella typhimurium*[a]

| Type of Assay | Strains of *Salmonella Typhimurium* | | | | | | | | | | | | | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S-9 | TA98 | TA1530 | TA1535 | TA1537 | TA1538 | TA1532 | TA1950 | TA1975 | TA1978 | G46 | TA100 | TA1531 | TA1534 | |
| Spot test | +/- | NT | NT | 0 | 0 | 0 | 0 | NT | NT | NT | NT | NT | NT | NT | McCann, 1978 |
| Plate incorporation | +/- | NT | NT | 0 | 0 | 0 | 0 | NT | NT | NT | NT | NT | NT | NT | McCann, 1978 |
| Plate incorporation | NR | NT | NT | 0 | NT | 0 | NT | NT | NT | NT | NT | NT | NT | NT | Nebert et al., 1976 |
| Plate incorporation[b] | +/- | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NT | NT | Gilbert et al., 1980 |
| Fluctuation | +/- | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NT | NT | Gilbert et al., 1980 |
| Spot test | - | NT | 0 | NT | NT | NT | + | NT | NT | NT | 0 | NT | QR | QR | Seiler, 1973 |
| Plate incorporation | + | 0 | NT | 0 | 0 | 0 | NT | NT | NT | NT | NT | 0 | NT | NT | Geiger and Neal, 1981 |
| Plate incorporation | - | NT | NT | NT | 0 | NT | NT | NT | NT | NT | NT | NT | NT | NT | Geiger and Neal, 1981 |
| Suspension assay | - | NT | 0 | NT | NT | NT | + | NT | NT | NT | NT | NT | NT | NT | Hussain et al., 1972 |

[a]Source: U.S. EPA, 1984a

[b]The assay was performed under both aerobic and anaerobic conditions.

NT = Not tested; NR = not reported; QR = questionable response; + = positive result; 0 = negative result

and the evidence for activity in short-term tests to be "inadequate." Applying the criteria for evaluating the overall weight of evidence for carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), 2,3,7,8-TCDD is most appropriately classified a Group B2 - Probable Human Carcinogen.

## 5. REGULATORY STANDARDS AND CRITERIA

Canada established a limit of 20 ppt 2,3,7,8-TCDD (20 ng/kg fish) in the Lake Ontario commerical fish exported to the United States. This limit was chosen to comply with an FDA determination that 2,3,7,8-TCDD levels <25 ppt (25 ng/kg fish) in fish pose no serious health concern (Food Drug Cosmetic Law Reports, 1981).

The National Academy of Sciences Committee on Drinking Water and Health (NAS, 1977) proposed an ADI of $10^{-4}$ µg 2,3,7,8-TCDD/kg bw/day, based on a 13-week rat feeding study (Kociba et al., 1976). This ADI was proposed before convincing evidence for the carcinogenicity of 2,3,7,8-TCDD had been obtained. The U.S. EPA is considering criteria of $1.3 \times 10^{-7}$, $1.3 \times 10^{-8}$ or $1.3 \times 10^{-9}$ µg 2,3,7,8-TCDD/ℓ (corresponding to excess cancer risks of $10^{-5}$, $10^{-6}$ or $10^{-7}$) in ambient waters, based on an assumed daily consumption of 6.5 g of contaminated fish and shellfish and 2 ℓ of drinking water (U.S. EPA, 1984b).

Kimbrough et al. (1983) recommended unofficially that contamination in soil limited to 1 ppb in residential areas would result in intake of 2,3,7,8-TCDD <126 pg/day, considered to be tolerable for a 70 kg human.

The New York State Dept. of Health has unofficially proposed 10 ppt in fish as a ceiling level for safe human consumption (DEC, 1985).

# 6. RISK ASSESSMENT

## 6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

2,3,7,8-TCDD has been demonstrated to be carcinogenic in laboratory animals and data are sufficient for estimation of carcinogenic potency. It is inappropriate, therefore, to derive an AIS for this chemical.

## 6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

2,3,7,8-TCDD has been demonstrated to be carcinogenic in laboratory animals and data are sufficient for estimation of carcinogenic potency. It is inappropriate, therefore, to derive an AIC for this chemical.

## 6.3. CARCINOGENIC POTENCY ($q_1^*$)

6.3.1. Oral. A number of bioassays have clearly demonstrated the carcinogenicity of 2,3,7,8-TCDD in experimental animals (see Table 4-1). These studies have recently been reviewed by the U.S. EPA (1984b). Human carcinogenic potency factors ($q_1^*$) were estimated from the study of Kociba et al. (1978) and the NCI bioassay (NTP, 1980). The highest $q_1^*$ obtained [$1.56 \times 10^5$ $(mg/kg\ bw/day)^{-1}$] was based on a review of the Kociba et al. (1978) study (U.S. EPA, 1984b). This $q_1^*$ was derived from the dose-response data for tumors of the liver, lung, hard palate and/or nasal turbinates in female rats. The data used in the derivation of this $q_1^*$ are presented in Appendix B.

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## APPENDIX A

Summary Table for 2,3,7,8-TCDD

| Carcinogenic Potency | Species | Experimental Dose/Exposure | Effect | Unit Risk or $q_1^*$ | Reference |
|---|---|---|---|---|---|
| Inhalation | | | | ND | |
| Oral | rat | $1x10^{-6}$-$1x10^{-4}$ mg/kg bw/day | tumors of the liver, lung, hard palate, and/or nasal turbinates | $1.56x10^{5}$ $(mg/kg/day)^{-1}$ | Kociba et al., 1978; U.S.EPA, 1983b |

ND = Not derived

## APPENDIX B

Data Used as a Basis for the $q_1^*$[a]

| | |
|---|---|
| Species, strain, sex = | Rats, Sprague-Dawley, female |
| Body weight (measured) = | 0.370 kg |
| Length of exposure = | 720 days |
| Length of experiment = | 720 days |
| Lifespan = | 720 days |
| Tumor site/type (one or more) = | squamous cell carcinomas of the lung, nasal turbinate and hard palate; neoplastic nodules and hepatocellular carcinomas of the liver |

| Dose (mg/kg/day) | Incidence (No. responders/No. tested) |
|---|---|
| 0.0 | 16/86 |
| $0.001 \times 10^{-3}$ | 8/50 |
| $0.1 \times 10^{-3}$ | 27/50 |
| $0.1 \times 10^{-3}$ | 34/47[b] |

[a]Source: A reanalysis of the Kociba et al. (1978) study by Dr. Robert Squire of Johns Hopkins University (U.S. EPA, 1984a).

[b]This dose-response point was dropped because of a poor fit to the linearized multistage model.